Synthesis of HOPO chelators for applications in separations of radionuclides, nuclear medicine imaging, and therapy.

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Abstract

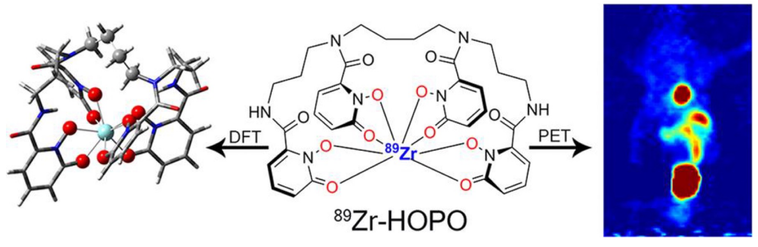
The synthesis of organic ligands plays an important role in all fields of radiochemistry including separations and nuclear medicine. For these applications, the chelator 3,4,3- L1(1,2 HOPO) is found to have strong selectivity and binding affinity to metals that are oxophilic with oxidation states of +4 and +3. In this work, the synthesis of 3,4,3- L1(1,2 HOPO), 3,3,3- L1(1,2 HOPO), and 3,2,3- L1(1,2 HOPO) was carried out. These chelators all bear four hydroxypyridinone (HOPO) groups but differ in the length of the carbon backbone chain and that difference may impact the binding and selectivity with +3 and +4 charged radiometal ions. We are synthesizing the three chelators and performing high-performance liquid chromatography, HPLC, to purify the chelators. Following that, we plan to test the binding affinity of the three chelators to metals such as Zr, Sc, and Lu and their radiometal analogs.

Purpose

- Synthesize and check the efficiency of 3,3,3- L1(1,2 HOPO), and 3,2,3- L1(1,2 HOPO) compared to 3,4,3- L1(1,2 HOPO).
- Purifying the chelators using high performance liquid chromatography.
- To test the binding affinity of the three chelators.

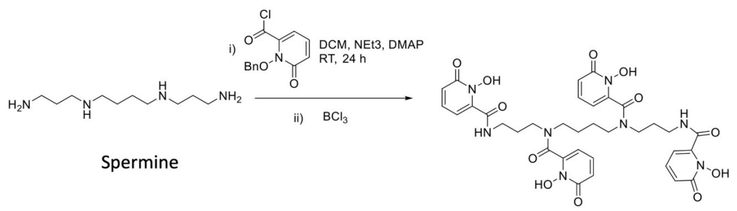
Introduction

- Zirconium- 89 is a successful radionuclide for antibody-based PET (positron emission tomography) imaging since its physical half life matches the biological half life of IgG antibodies. Since antibodies possess half lives of over three days, images are able to be captured multiple days after injection. Furthermore, since zirconium-89 has a relatively low energy positron, images have higher resolution.
- Currently deferrioxamine B (DFO) is the preferred chelator for +4 zirconium- 89, however it is predicted that $^{89}Zr^{+4}$ is released from DFO in vivo. This is very concerning as the accumulation of $^{89}Zr^{+4}$ in the bone could increase radiation dose to the bone marrow.
- The chelator HOPO, on the other hand, is an octadentate chelator with a spermine backbone coupled with four hydroxypyridinone groups for metal bonding.
- The hydroxypyridinone groups offer hard oxygen donor groups. This with its eight-coordination binding offers good in vivo stability and should be an ideal coordination environment for Zr^{+4}.

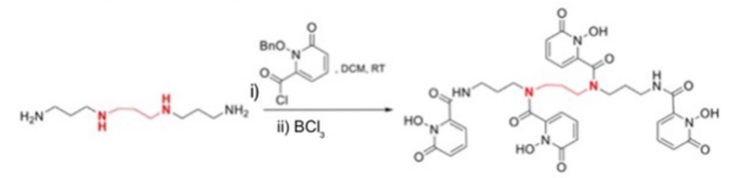


Synthesis

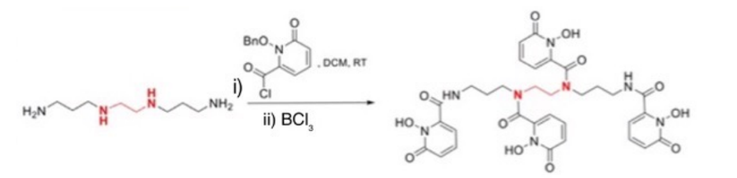
Synthesis of 3,4,3- L1(1,2 HOPO):



Synthesis of 3,3,3- L1(1,2 HOPO):



Synthesis of 3,2,3- L1(1,2 HOPO):



When compared to the first reaction shown, 3,4,3- L1(1,2 HOPO), the difference in the length of the carbon backbone chain following 3,3,3- L1(1,2 HOPO) and 3,2,3- L1(1,2 HOPO) can be seen in red.

Conclusions

- The synthesis of 3,2,3- L1(1,2 HOPO) is 100 times less expensive than spermine, which could be very beneficial when trying to produce on a large scale.
- When compared to DFO, HOPO remains to be a superior ligand.

Future Work

- Synthesize macroscopic Zr, Sc and Lu complexes and characterize these.
- Synthesize the radiometal ^{89}Zr, $^{44/47}Sc$ and ^{177}Lu complexes and verify their structure and speciation by HPLC co-elution studies.
- Examine the stability of the radiometal complexes: in serum, to challenges using EDTA, and to challenges using endogenous metal ions such as Cu^{2+}, Fe^{3+}, Zn^{2+}.

References

- Durbin et al. Int. J. Radiat. Biol. 2000, 76, 199.
- Guilmette et al. Radiat. Prot. Dosim. 2003, 105, 527-534
- Gorden et al. Chem. Rev. 2003, 103, 4207-4282
- Deri et al. *J. Med. Chem.* 2014, 57, 4849-4860

Acknowledgements

- This work was supported in part by Department of Energy Isotope Program's Grant DE-SC0022550, the Horizon-broadening Isotope Production Pipeline Opportunities (HIPPO) program.

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